

# Which is better for pain reduction during transrectal ultrasound-guided biopsy of the prostate: Intravenous diazepam, local periprostatic nerve block, or combination? controlled randomized study

## ABSTRACT

**Background:** Transrectal ultrasound-guided prostate biopsy (TRUSPB) is considered the procedure of choice for the diagnosis of prostate cancer. Men undergoing this biopsy experience high psychological stress. Different studies recommend techniques as sedation, lidocaine gel intrarectally, periprostatic nerve block alone, or nitrous oxide inhalation as effective methods of analgesia during procedural-related pain or discomfort. We evaluated three techniques for pain relief during TRUSPB and evaluated if there was any increase in the incidence of complications when employing either technique.

**Setting:** Assiut University Hospital, Assiut, Egypt.

**Methods:** Three hundred patients of age 43–92-year-old underwent TRUSPBs. Patients were allocated randomly into three equal groups to receive intravenous (IV) diazepam 5 mg slowly (Group I), bilateral periprostatic nerve block by 10 ml of 1% lidocaine solution injected under ultrasound guidance (Group II), or combined IV diazepam and the periprostatic nerve block (Group III).

**Results:** The mean pain score was 4.95 for patients in Group I, 4.15 for patients in Group II, and 2.18 for patients in Group III with statistically significant findings ( $F = 120.27$ ,  $P < 0.001$ ). TRUSPB under combined IV sedation and local anesthesia had no significant increase in the incidence of complications.

**Conclusions:** Patients should have analgesia during TRUSPB to decrease the procedure pain and to improve tolerance permitting proper aiming for biopsy cores without increasing the patient distress. The combined IV sedation and local periprostatic nerve block are efficient in controlling and limiting pain better than employing each technique alone with no significant increase in complications incidence.

**Key words:** Analgesia; biopsy; cancer; prostate

## Introduction

Transrectal ultrasound-guided prostate biopsy (TRUSPB) is considered the procedure of choice for the diagnosis of

prostate cancer.<sup>[1]</sup> TRUSPB is usually performed in outpatient clinics and men undergoing this biopsy experience high

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psychological stress,<sup>[2]</sup> may be due to the fear of potential cancer diagnosis or the anal route of penetration.<sup>[3]</sup>

Thus, it is important to develop a simple method to liberate patients from pain during the biopsy. Different studies recommend techniques as sedation, lidocaine gel intrarectally, periprostatic nerve block alone, or nitrous oxide inhalation as effective methods of analgesia during procedural-related pain or discomfort.<sup>[1,4]</sup> When systemic medication is administered, patients require cautious monitoring, which may be inconvenient and relatively expensive.<sup>[5]</sup>

Old studies examined the benefit of local pain control during TRUSPB resulted in controversial findings, regardless of the method of local anesthetic used.<sup>[6]</sup> For our own knowledge, it is the first time to discuss the combined role of intravenous (IV) sedation and local periprostatic nerve block for analgesia during prostate biopsy.

### Objectives

We postulated this study to compare the feasibility and efficacy of the IV sedation versus periprostatic nerve block or their combination.

### Methods

#### Eligibility and randomization

With respect to the principles of the Declaration of Helsinki, 300 patients fitted our inclusion criteria underwent TRUSPB, from November 2013 to November 2014. Written informed consents were obtained from all patients before enrollment in the study, after a detailed description of the study. This prospective controlled computer-generated randomized study has been approved by the Institutional Review Board of Faculty of Medicine, Assiut University, Egypt (Ref: 00008718) and registered with Clinical Trials (Ref: NCT02935972).

#### Sample size calculation

Sample size calculation was based on the pilot study, where the intervention that can cause 50% reduction in pain incidence after TRUSPB was interesting. With a power of 90% and type I error of 5%, 93 patients were required to be in each group ( $\alpha = 0.05$  and  $\beta = 90\%$ ); however, to avoid possible loss of samples (dropouts) during the study, the number of patients in each group was increased to 100.

#### Setting

Assiut University Hospital, Assiut, Egypt.

#### Inclusion criteria

Indications for biopsy included abnormal digital rectal examination, elevated prostate-specific antigen (PSA), or focal abnormality in transrectal ultrasound (TRUS).

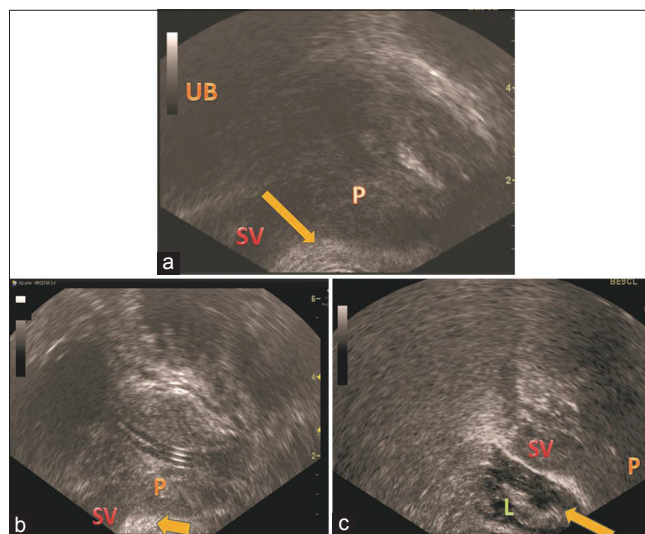
#### Exclusion criteria

Patients with previous allergy to diazepam or lidocaine, bleeding diathesis, anticoagulant therapy, history of chronic prostatitis, acute anal or rectal conditions (as hemorrhoids, anal fissures, or strictures), neurological conditions, respiratory asthma, or chronic liver diseases were excluded from the study.

#### Technique

Good bowel preparation with a cleansing enema (a sodium phosphate and dibasic sodium phosphate enema) and antibiotic prophylaxis with levofloxacin 500 mg were prescribed. Patients were randomized into three equal groups where Group I received IV diazepam 5 mg slowly 3–5 min just before probe insertion, Group II received 10 ml of 1% lidocaine injected into the periprostatic nerve plexus bilaterally under ultrasound guidance using a 22-gauge 7-inch needle. Before injection, caution was taken to aspirate to avoid accidental intravascular injection of lidocaine. For proper needle placement and injection of lidocaine, a sonographic hypoechoogenicity was created between the rectal wall and the base of the seminal vesicles causing the seminal vesicles to separate from the rectal wall and appear to be raised [Figure 1]. Prostate biopsies had begun 2–3 min after lidocaine injection.

Group III received diazepam 5 mg slowly and 10 ml of 1% lidocaine injected into the periprostatic nerve plexus bilaterally under ultrasound guidance, 3–5 min just before probe insertion.



**Figure 1:** Site for periprostatic lidocaine injection "Mount Everest sign" (arrow) is white pyramid identified in the sagittal plane created by hyperechoic fat in the notch between seminal vesicle (SV) and prostate (P) laterally. (b) Sagittal image pre-injection of periprostatic lidocaine. (c) Sagittal image post injection of periprostatic lidocaine, the signs of proper injection with a hypoechoic wheel and apparent elevation of the SV

Prostatic biopsies were performed in combined directed and random technique or extended random technique in the absence of focal abnormality with a mean number of biopsies 10 biopsies (9–12 biopsies) per patient.

The sedation scale was evaluated according to the following sedation scale: Score 1: no response to shaking, Score 2: responds only to shaking, Score 3: responds only to name call loudly, Score 4: lethargic response to name spoken in normal tone, and Score 5: responds readily to name spoken in normal tone.

After the procedure, discomfort and pain experienced during performing the biopsy technique were graded using the 10-point linear visual analog pain scale [Figure 2].

All patients were monitored during and after the whole procedure for vital signs and any possible complication. Patients were questioned regarding any adverse effect at 1-week duration (at the time of receiving the histopathological results). Patients' satisfaction was also recorded.

### Statistical analysis

Data were analyzed using the SPSS (SPSS Inc., Chicago, Illinois, USA) version 20. Numerical variables were compared among the three groups using the Kruskal–Wallis test followed by the Mann–Whitney test. Categorical variables were compared among the three groups using the Chi-square test followed by Fisher's exact test. Results were considered statistically significant when  $P < 0.05$ .

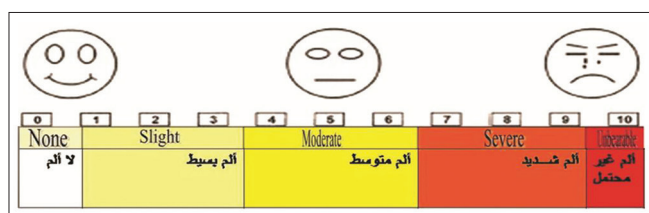


Figure 2: Linear visual analog pain scale

Table 1: Patient characteristics of the patients

Variable	Group I (n=100)	Group II (n=100)	Group III (n=100)	P
Age				
Range	43-82	49-92	44-82	NS
Mean ± SD	61.4 ± 8.7	62.1 ± 9.1	62.5 ± 9.7	
Mean PSA (mean)	11.7	11.5	11.7	NS
Mean prostate volume (ml)	30 ± 13.2	36 ± 16.4	29 ± 14.6	NS
Sum number of biopsy cores (mean ± SD)	1092 (9.7 ± 3.2)	1107 (9.8 ± 3.3)	1094 (9.7 ± 3.3)	NS
Number of cases positive for malignancy (%)	50 (50)	28 (28)	44 (44)	NS
Average duration (min)	12-14	13-15	12-15	NS

NS: Not significant; SD: Standard deviation; PSA: Prostate specific antigen

## Results

Three hundred patients were enrolled in our study, randomized into three equal groups including 100 patients each. Patients' age ranged from 43 to 82 years (mean  $61.4 \pm 8.7$ ) in Group I, 49–92 years (mean  $62.1 \pm 9.1$ ) in Group II, and 44–82 years (mean  $62.5 \pm 9.7$ ) in Group III with no statistically significant difference [Table 1].

Regarding the PSA level, there was no statistically significant difference regarding the mean value ( $F = 0.02$ ,  $P = 0.998$ ) as it was 11.7, 11.5, and 11.7 ng/ml for the Groups I, II, and III, respectively.

The mean prostate volume for Group I was  $30 \pm 13.2$  ml; for Group II, it was  $36 \pm 16.4$  ml; and that of Group III, it was  $29 \pm 14.6$  ml without any statistically significant difference ( $F = 1.65$ ,  $P = 0.195$ ).

The injection of local anesthetic agent was completed in <1 min in all patients of Groups II and III; no additional time delay before proceeding to biopsy in any case where the average procedure time was 12–14 min (mean = 13) for Group I, 13–15 min (mean = 14) for Group II, and 12–15 min (mean = 14) for Group III, followed by bimanual compression for 1 min in all patients.

Mean prostatic biopsy cores in patients groups were  $9.7 \pm 3.2$  for Group I,  $9.8 \pm 3.3$  for Group II, and  $9.7 \pm 3.3$  for Group III with no statistically significant difference ( $P = 0.897$ ).

Pathological findings revealed positive results for malignancy in fifty patients (50%) in Group I, in 28 patients (28%) of Group II, and in 44 patients (44%) of Group III.

In all cases, vital signs were determined before, during, and after the biopsy. All patients had readings within normal values regarding vital signs.

The sedation scale in patients of Groups I and III was ranging from 2 to 4 according to sedation scale with the mean scale of 3.

Mean pain score in these patients was  $4.95 \pm 1.1$  for Group I,  $4.1 \pm 1.37$  for Group II, and  $2.18 \pm 1.6$  for Group III. Statistical analysis using analysis of variance showed that there was a statistically very high significant difference regarding the pain score in the three groups ( $F = 120.27$  with  $P < 0.001$ ) [Table 2].

There were no noted patients' complications due to local anesthetic injection as significant rectal wall hematoma, excessive rectal or urethral bleed, or evident lidocaine toxicity. Patients were followed up after 1 week, none of them had complained of persistent hematuria or rectal bleeding lasting more than 5 days. No major infectious complications that would require hospitalization were encountered. No statistically significant findings were found to occur in the study groups due to the mode of anesthesia employed. No symptoms or signs of lidocaine or diazepam toxicity or overdosage were found [Table 3].

## Discussion

TRUSPB has been a time-tested procedure in terms of effectiveness and side effects.<sup>[7,8]</sup> This procedure can safely be performed without any local anesthesia in a significant proportion of patients. The use of local anesthesia is controversial; in some opinions, its employment should be individualized at least to improve psychological patient reassurance in rare patients who may experience considerable difficulty in tolerating the procedure.<sup>[6]</sup>

**Table 2: Visual analog scale and patients' satisfaction**

Variable	Group I (n=100)	Group II (n=100)	Group III (n=100)	P
Pain score (mean±SD)	4.95±1.1	4.1±1.37	2.18±1.6	<0.001
Patients' satisfaction (%)				
Yes	98 (87.5)	86 (76.8)	101 (90.2)	0.004
No	14 (12.5)	26 (23.2)	11 (9.8)	

SD: Standard deviation

**Table 3: Complications encountered in the study**

Complications of biopsy	Group I (n=100)	Group II (n=100)	Group III (n=100)	P
Immediate insignificant hematuria (n)	34	22	32	NS
Immediate insignificant hematochezia (n)	8	17	6	NS
Minor infectious complications (n)	5	1	3	NS

NS: Not significant

Others believe that men should have the opportunity to receive local anesthesia before TRUSPB aiming to decrease discomfort associated with this procedure.<sup>[5]</sup>

Pain associated with TRUSPB is thought to originate predominantly from the prostate capsule or stroma, where there is a rich network of autonomic fibers. These autonomic nerves convey visceral sensation to the spinal cord. Innervation of the prostate is derived from the caudal roots of S2–S5 and the sympathetic chain through the presacral and hypogastric neural plexus. These fibers ramify in the prostatic vascular pedicles, which are located at the posterolateral aspect of the prostate base.<sup>[4]</sup>

Another source of pain during the prostate biopsy is the rectum, where the sensory innervation is below the dentate line.<sup>[9]</sup> However, as biopsy needle pierces the rectal wall in an area of decreased sensorium (above the dentate line), most pain provoked by the biopsy needle is considered to originate in the prostate.<sup>[3]</sup>

The most commonly used procedures for pain control during TRUSPB are the local application of lidocaine either by intrarectal lidocaine gel or periprostatic lidocaine injection<sup>[1,10]</sup> and sedation.<sup>[11]</sup> Many studies evaluated the intrarectal lidocaine gel use versus periprostatic lidocaine injection or IV sedation alone; for our own knowledge, this was the first study done to compare the combined IV sedation and periprostatic lidocaine injection.

IV sedation significantly reduced discomfort, fear of introduction of the probe, and alleviated patient anxiety. While the periprostatic nerve block by infiltrating lidocaine at each side of the apex is sufficient to control pain, the lidocaine bolus extends under the Denonvillier's fascia up to the lateral borders of the prostate and the seminal vesicle-prostatic angles.<sup>[11]</sup>

The improved patient tolerance achieved by effective anesthesia permitted the number of biopsy cores to be increased as necessary without increasing patient's distress.

Our results are quite similar to Rodriguez *et al.*,<sup>[11]</sup> Alavi *et al.*,<sup>[5]</sup> Wu *et al.*,<sup>[12]</sup> Seymour *et al.*,<sup>[13]</sup> Leibovici *et al.*,<sup>[3]</sup> and Mallick *et al.*<sup>[14]</sup> that show the effectiveness of periprostatic nerve block ( $P < 0.001$ ).

However, our study showed an increased mean pain score than that recorded in studies of Peters *et al.*,<sup>[11]</sup> Turgut *et al.*,<sup>[15]</sup> Ozok *et al.*,<sup>[16]</sup> and Song *et al.*<sup>[17]</sup> This may be attributed to different drugs employed in IV sedation [Table 4].

**Table 4: Comparison of randomized prospective studies handling the methods of anesthesia for sonographic-guided prostatic biopsies**

Prospective published studies	Total number of patients	Placebo pain score	Intrarectal 2% lidocaine gel pain score	Periprostatic 1% lidocaine solution infiltration pain score	IV sedation	Significance (P)
Rodriguez <i>et al.</i> <sup>[11]</sup>	96		2.76	1.73		0.001
Alavi <i>et al.</i> <sup>[5]</sup>	150		3.7	2.4		0.00002
Wu <i>et al.</i> <sup>[12]</sup>	40	1.6		1.2		0.77
Seymour <i>et al.</i> <sup>[13]</sup>	157	1.95		1.53		0.001
Leibovici <i>et al.</i> <sup>[3]</sup>	90	4.15		3.06		0.04
Issa <i>et al.</i> <sup>[10]</sup>	50	5	2			0.00001
Mallick <i>et al.</i> <sup>[14]</sup>	328		0.8	1.4		0.001
Peters <i>et al.</i> <sup>[11]</sup>	100				1.5	<0.05
Turgut <i>et al.</i> <sup>[15]</sup>	93			2	1.4	<0.05
Ozok <i>et al.</i> <sup>[16]</sup>	100				1	<0.001
Song <i>et al.</i> <sup>[17]</sup>	104					<0.05
Current study	300			4.1	4.95	<0.001

IV: Intravenous

Furthermore, this study aimed to assess if there is an increase in the incidence of complications when employing either method. There were no noted patients' complications due to anesthesia injection as rectal wall hematoma, excessive rectal or urethral bleed, or evident lidocaine toxicity or complications due to IV sedation. No statistically significant findings were found to occur between the study groups due to the mode of anesthesia employed. Our results are quite similar to Obek *et al.*<sup>[18]</sup> and Desgrandchamps *et al.*<sup>[19]</sup> where there was no anesthesia-related increased incidence of complications.

Our study contained few limitations in our opinion (that will be tried to be avoided in the future studies) as first: making the number of biopsies the same in each group of patients, however, the average biopsy technique employed was 9–12 biopsy cores. The mean number of biopsies was calculated with no statistical difference; however, fixing number of biopsy per patient is a very difficult matter as the biopsy regimen is tailored on each case according to TRUS findings.

Second: the assessment of lidocaine toxicity was evaluated on clinical basis only; lidocaine toxicity should be accurately evaluated by evaluation of plasma levels of lidocaine after TRUS biopsy (as the accepted levels when lidocaine is used for regional nerve blocks, plasma levels are usually 3–5 µg/ml while toxicities may be observed at 6 µg/ml, but more commonly occur once levels exceed 10 mcg/ml).<sup>[20]</sup>

Third: in spite of midazolam has been the most widely used sedative premedication because of its short half-life, faster onset of sedation, and excellent sedative hypnotic effect without any significant side effects, such as vasculitis.<sup>[18]</sup> However, we used diazepam as it is more available and less expensive, especially for patients in the outpatient clinics.

## Conclusions

Patients should have pain relief measures during TRUSPB to decrease the procedure pain and improve patient tolerance permitting proper aiming for biopsy cores and increasing the number of biopsy cores without increasing the patients' distress. The combined IV sedation and local periprostatic block are more efficient in controlling and limiting pain better than employing each technique alone with no significant increase in complications incidence.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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